Placebo-Controlled Trials

Summary: To examine critically the ethical issues associated with the use of placebo controls in clinical trials, to develop a systematic framework for analyzing the conditions under which the use of placebo controls is ethical, and to define appropriate safeguards for protecting participants in placebo-controlled trials.

Section: Human Subject Research – Unit on Clinical Research

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Background: Randomized controlled trials (RCTs) became the leading method of testing treatment efficacy in the 1940s. From the beginning, ethical concerns were voiced about clinical trials involving control groups not receiving proven effective or standard treatment. Recent debate over the use of placebo controls intensified following the publication in 1994 of a *New England Journal of Medicine* article by Rothman and Michels, "The Continued Unethical Use of Placebo Controls." The authors appealed to the Declaration of Helsinki—the leading international code of ethical requirements for clinical research—in support of their claim that placebo-controlled trials are unethical whenever they are used to evaluate new treatments for conditions when proven effective treatments exist. They cited a range of recently reported placebo-controlled trials in the medical literature that violated the ethical guidance of the Declaration of Helsinki. Additionally they pointed to the regulatory policy of the United States Food and Drug Administration as a major reason for the continued unethical use of placebo controls.

The prevailing ethical position on placebo controls is that it is unethical to compare a new treatment for a disorder with placebo in a clinical trial if proven effective treatment exists for that disorder. It is claimed that the use of placebo controls when proven effective treatment exists violates the duty of physicians to offer optimal medical care. Because patients who enroll in RCTs are seeking treatment, they should not be randomized to treatment known to be inferior. Instead, experimental treatments should be tested against standard, proven effective treatment. The leading ethical argument against the use of placebo

controls in the face of proven effective treatment invokes the principle of "clinical equipoise," initially formulated by Benjamin Freedman in 1987. What makes it ethical to conduct an RCT comparing a new treatment with standard treatment, but not with placebo, is that experts in the clinical community are uncertain or in a state of disagreement about whether the new treatment is as good or better than standard therapy. Use of placebo controls in the face of proven effective treatment violates clinical equipoise because it is already known that placebo is inferior to standard treatment.

Underlying both clinical equipoise and the therapeutic obligation of physicians is the principle of therapeutic beneficence, central to medical ethics. Physicians should promote the medical best interests of patients by offering optimal medical care; and the risks of prescribed treatments are justified by the potential therapeutic benefits to patients receiving them. Patients randomized to placebo forgo proven effective treatment or treatment with a novel intervention considered to be as good as or better than standard treatment. Accordingly, they are exposed to risks associated with lack of treatment that are not justified by potential medical benefits, thus contravening the principle of therapeutic beneficence.

Despite the bioethical orthodoxy that RCTs should be governed by clinical equipoise, placebo-controls have continued to be widely used in clinical trials of novel treatments of conditions for which proven effective treatment exists, including psychiatric disorders, migraine headaches, asthma, hypertension, and stable angina. Proponents of these placebo-controlled trials have argued that the use of placebo is ethical as long as trial participants are not exposed to risks of serious, irreversible harm from the temporary withholding of treatment. Led by Robert Temple of the FDA, they have argued that the major alternative to the use of placebo controls in these situations—the active-controlled equivalence trial—is subject to serious methodological problems. The finding that there is no statistically significant difference between a new and an established treatment does not imply that the new treatment is effective. It remains possible that neither the new nor the control treatment were effective in this particular trial. Trials of psychiatric disorders in which both the experimental agents and standard drugs fail to beat placebo are common. This risk of a "failed" trial pertains especially to conditions with high rates of placebo response. Therefore, active-controlled equivalence trials are not able to demonstrate efficacy definitively unless the control treatment has consistently proved superior to placebo in previous trials. It is argued that failure to use placebo controls in many conditions for which effective treatments exist would lead to the licensing or validation of new treatments that in fact are no better than placebo.

A different ethical controversy over placebo controls concerns the use of "sham surgery" to evaluate rigorously new or currently administered surgical procedures. Surgical procedures are routinely introduced into practice without rigorous testing and have rarely been compared to sham surgery, owing to

ethical concerns about the use of an invasive placebo control. Ethical debate was sparked in 1999 by trials that evaluated the injection of fetal neural tissue into the brains of severely ill patients with Parkinson's disease by comparing this experimental treatment with a sham procedure involving burr holes drilled into the skulls of trial participants under general anesthesia. Based on ethical analyses of this trial, the use of sham surgery has been widely condemned in the bioethics community.

Objectives:

(1) To evaluate critically the ethical arguments for and against the use of placebo controls when proven effective treatment exists for the disorder under investigation or when the use of the placebo itself carries risks to trial participants.
(2) To develop and justify criteria for the ethical use of placebo controls.
(3) To delineate appropriate safeguards for the protection of participants in placebo-controlled trials.
(4) To develop an approach to the ethical evaluation of clinical trials that is based on recognition of the significant differences between medical care and clinical research.

Methodology: The literature on the ethics and methodology of placebo-controlled trials was reviewed, and published reports of numerous placebo-controlled trials were examined. To guide ethical analysis, a 3-part typology of cases was developed encompassing trials in which placebo assignment poses (1) at most minor risks; (2) temporary mild to moderate dysfunction and discomfort; and (3) serious risks of severe harm or intolerable discomfort.

Results: The Department began work on this project with an examination of placebo-controlled trials in psychiatric disorders. Although the leading ethical arguments against the use of placebo controls when proven effective treatments exist appeared to be solidly grounded, practical and theoretical weaknesses emerged after careful reflection on methodological considerations of study design. The simplistic claim voiced by some prominent critics of placebo-controlled trials that science should not be given priority over ethics implies a false dichotomy. Because scientific validity is a basic ethical requirement of clinical research, it is unethical for trial participants to be exposed to the risks of studies lacking sufficient rigor to produce valid results. As a rule, active-controlled equivalence trials lack internal validity, which is especially problematic in trials of symptomatic treatments of chronic conditions with waxing and waning symptoms and high rates of placebo response, such as mood and anxiety disorders. Accordingly, validating new treatments that appear not to be inferior to existing treatments in active-controlled trials could lead to the widespread use of treatments that in fact lack efficacy. Prohibition of placebo-controlled trials when proven effective treatments exist, therefore, could have serious negative consequences.

On closer examination, clinical equipoise was seen as conflating the ethics of clinical research with the ethics of clinical medicine by misapplying the principle of therapeutic beneficence to the significantly different context of clinical trials. Clinical trials are designed to test hypotheses about treatment efficacy in groups of patients; they are not designed to provide optimal personalized medical care for individual patients. When the nature of clinical trials as scientific experiments is taken as central to ethical thinking about trial design, then clinical equipoise becomes questionable. It is not necessarily unethical for trial participants randomized to placebo to forgo either proven effective or experimental treatment. What counts ethically is not whether patients are "denied" treatment in a placebo-controlled trial, but whether placebo assignment exposes them to risks of serious harm. The risks of placebo controls when proven effective treatment exists should be seen in the same way as the risks of nontherapeutic procedures in clinical research aimed at improving the understanding of medical disorders.

Critical scrutiny also called into question a second argument against placebo-controlled trials: when proven effective treatment exists for a given condition, there is no scientific or clinical merit in testing whether a new treatment is better than placebo. According to this argument, the valuable question is whether the new treatment is as good or better than standard treatment. However, with the exception of those situations in which active-controlled equivalence trials can produce valid results, no new treatment should be licensed or validated without being shown to be *superior* to a control intervention (either placebo or active comparator) in one or more RCTs. Because placebo-controlled trials typically require smaller sample sizes, they are more efficient than active-controlled trials, making them desirable in the initial efficacy trials of new treatments, provided that short-term lack of effective treatment does not pose undue risk of harm. Definitive demonstration that a novel treatment is effective via a well-powered placebo-controlled trial has both scientific and clinical merit. Once a new treatment is validated by being shown to be superior to placebo, placebo controls may remain methodologically indicated in 3-way trials to produce a valid comparison between the new and standard treatment.

The Department's initial ethical analysis of placebo-controlled trials that withhold proven effective treatment in psychiatric research concluded that these studies can be ethical if they have scientific merit, if the risks are not excessive and justifiable by the knowledge to be gained from the trial, and participants give informed consent. Members of the Department next developed a more comprehensive, "middle ground" position on the ethics of placebo-controlled trials. Advocates of placebo-controlled trials were criticized for failing to offer clear and consistent statements about when the use of placebo is ethical, and for taking too narrow a view of the harms that would make placebo assignment unethical. Focusing solely on the irreversible harms of mortality and serious morbidity from nontreatment neglected reversible harms of temporary

dysfunction and severe suffering. Opponents of placebo-controlled trials were criticized for failing to give due attention to the methodological weaknesses of active-controlled equivalence trials, and for taking an absolutist stance that would unreasonably rule out placebo-controlled trials for new treatments of conditions, such as allergic rhinitis, in which short-term lack of treatment due to placebo assignment would be unlikely to pose any serious risks of harm. Additionally, it was demonstrated that active-controlled trials, which typically require larger sample sizes, could expose more participants to the harm of nonresponse than comparable placebo-controlled trials when the new treatment proves less effective than the standard active comparator. Criteria were advanced for determining when placebo-controlled trials are ethical: (1) there must be compelling methodological reasons in favor of the use of placebo controls; (2) those exposed to the placebo control should not be more likely than those receiving active treatment to suffer serious harm or discomfort; and (3) adequate safeguards must be in place to protect the rights and welfare of trial participants.

In order to spark debate in the bioethics community, the leading ethical arguments against the use of placebo-controlled trials when proven effective treatment exists were challenged in a "target article," published in the *American Journal of Bioethics*, accompanied by 15 short commentaries. The Department also undertook two additional inquiries concerning the ethics of placebo-controlled trials. The first analyzed the unethical use of placebo-controls in certain asthma clinical trials, owing to the lack of a clear and compelling methodological rationale for placebo assignment. The second interpreted the federal regulations governing research with children to provide guidance on reviewing and approving pediatric placebo-controlled trials.

The Department also explored the ethical issues posed by the use of sham procedures to evaluate medical and surgical procedures. In contrast to pill placebos, sham procedures carry risks from the invasiveness of the placebo intervention. A systematic ethical analysis was undertaken which identified criteria for ethically justifiable sham-controlled procedure trials, including sham surgery. An article published in *The New England Journal of Medicine* on the ethics of sham surgery argued that the ethical objections to sham surgery, deriving from the requirement to minimize risks and concern about the use of misleading tactics to make participants believe that the sham intervention was a real surgery, did not support an absolute prohibition of sham-controlled surgery trials. Such trials can be ethically justified if the use of the sham control is methodologically required, and no more risky than necessary, to produce a rigorous test of study hypotheses; if the risks of the invasive placebo do not exceed a tolerable threshold and are justified by the knowledge to be gained from the trial; and adequate procedures are adopted to obtain the informed consent of participants, including disclosing in advance that misleading tactics will be used to maintain the authenticity of the trial. A manuscript presenting a more detailed ethical analysis of sham surgery for a bioethics audience is under review.

Based on this the ethics of placebo-controlled trials, a major focus of current conceptual research is how the ethics of clinical trials, and clinical research in general, differ from the ethics of medical care. This includes a detailed critique of clinical equipoise, drawing on the history of ethical thinking about clinical trials, and analysis of the theoretical and practical problems deriving from conflating the ethics of clinical research with the ethics of medical care.

Future Directions: An opportunity to synthesize work on the ethics of placebo-controlled trials is offered by the Department's textbook on human subjects research, which will contain a chapter on that topic. An anticipated future product of research over the next couple years is a book on the ethics of clinical research, consolidating the results of multiple conceptual inquiries and articulating an ethical framework that accounts for the important ways in which clinical investigation differs from patient care.

Publications:

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